Change in Albuminuria and eGFR Following Insulin Sensitization Therapy Versus Insulin Provision Therapy in the BARI 2D Study

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Summary

Background and objectives In the Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial, glycemic control with insulin-sensitization therapy was compared with insulin-provision therapy in patients with type 2 diabetes and coronary artery disease. This study examined differences in albumin excretion and renal function in the insulin-sensitization group versus the insulin-provision group over 5 years.

Design, setting, participants & measurements In total, 1799 patients with measurements of creatinine and urine albumin/creatinine ratio at baseline and at least two follow-up visits were included. Management of BP, lipids, and lifestyle counseling was uniform. Progression of albuminuria was defined as doubling of baseline albumin/creatinine ratio to at least 100 mg/g or worsening of albumin/creatinine ratio status on two or more visits. Worsening renal function was defined as >25% decline in estimated GFR and annualized decline of >3 ml/min per 1.73 m^2 per year.

Results By 6 months and thereafter, the mean glycated hemoglobin levels were lower in the insulin-sensitization group compared with the insulin-provision group ($P<0.002$ for each time point; absolute difference=0.4%). Albumin/creatinine ratio increased over time in the insulin-sensitization group (P value for trend<0.001) and was stable in the insulin-provision group. Risk for progression of albumin/creatinine ratio was higher in the insulin-sensitization group compared with the insulin-provision group (odds ratio, 1.59; 95% confidence interval, 1.25 to 2.02; $P=0.02$). Over 5 years, albumin/creatinine ratio increased from 11.5 (interquartile range=5.0–46.7) to 15.7 mg/g (interquartile range=6.2–55.4) in the insulin-sensitization group ($P<0.001$) and from 12.1 (interquartile range=5.3–41.3) to 12.4 mg/g (interquartile range=5.8–50.6) in the insulin-provision group ($P=0.21$). Estimated GFR declined from 75.0±20.6 to 66.3±22.6 ml/min per 1.73 m^2 in the insulin-sensitization group ($P<0.001$) and from 76.1±29.5 to 66.8±22.1 ml/min per 1.73 m^2 in the insulin-provision group ($P<0.001$).

Conclusion Over 5 years, despite lower glycated hemoglobin levels, the insulin-sensitization treatment group had greater progression of albumin/creatinine ratio compared with the insulin-provision treatment group. Decline in estimated GFR was similar.

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Introduction

Diabetes mellitus is a leading cause of CKD and ESRD. Strategies for reducing progression include controlling BP and glycemia (1–3). Lowering BP with renin angiotensin system blockade delays CKD progression in patients with type 2 diabetes mellitus (T2DM). Clinical trials comparing different glycemic control strategies have not shown renal benefits of one drug compared with another drug (4).

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) clinical trial of patients with angiographically documented stable coronary artery disease (CAD) and T2DM compared mortality and cardiovascular event rates in study participants randomized to two coordinate treatment strategies. One strategy directed to relieve ischemia compared early coronary revascularization and intensive medical therapy with initial intensive medical therapy alone with the option of revascularization, if needed, to relieve symptoms; the other strategy compared an initial strategy of insulin-sensitization (IS) therapy with insulin-provision (IP) therapy to manage hyperglycemia (5,6). Study participants were treated to achieve a target glycated hemoglobin level of <7%, irrespective of the regimen used.

Although baseline serum creatinine>2 mg/dl was an exclusion criteria, CKD was common in the BARI 2D trial; at enrollment, 43% of participants had reduced estimated GFR (eGFR), albuminuria, or both (7). Herein, we report the impact of the randomly assigned glycemic control strategies of IS therapy versus IP therapy used in the BARI 2D trial on changes

in eGFR and albuminuria in 1799 of 2368 study participants, in whom baseline data and 2 or more years of follow-up data on albumin/creatinine ratio (ACR) and eGFR were available.

Materials and Methods

Study Design

The BARI 2D study was conducted from 2001 to 2008 (ClinicalTrials.gov Identifier: NCT00006305). Details of study design (5), characteristics of the study population (8), baseline kidney function (7), and primary outcome (6) have been reported.

The study was approved by the Institutional Review Boards at each participating site and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent.

Glycemic Control Strategies

Patients randomized to IS therapy could be treated with metformin, rosiglitazone, or other thiazolidinediones at the discretion of the local site investigator. The IP regimen included sulfonylurea and insulin. If target glycated hemoglobin level of <7% was not achieved with the randomized strategy, the protocol allowed for addition of agents from the alternate strategy. The goal for LDL cholesterol was <100 mg/dl, and the goal for BP was 130/80 mmHg or less. All participants were counseled regarding smoking cessation, weight loss, and regular exercise.

Measurements

Serum creatinine level was measured locally at each study site. Information regarding coefficient of variation for each laboratory was not collected, and most sites did not switch to the isotope dilution mass-spectrometry traceable creatinine assay until the last year of the study. GFR was estimated using the abbreviated Chronic Kidney Disease Epidemiology Collaboration Equation (9). Reduced eGFR was defined as <60 ml/min per 1.73 m^2 (*i.e.*, stage 3 CKD). Worsening of eGFR was defined as a >25% reduction from baseline and an annualized eGFR decline>3 ml/min per year (10). Second void morning urine specimens were collected at baseline and annually, and they were assayed for creatinine and albumin at the University of Minnesota Core Biochemistry Laboratory. ACRs were calculated for each participant. Baseline albuminuria status was categorized as normal albuminuria (ACR<17 mg/g for men; ACR<25 mg/g for women), microalbuminuria (ACR≥17 and <250 mg/g for men; ACR≥25 and <355 mg/g for women), or macroalbuminuria (ACR≥250 mg/g for men; ACR≥355 mg/g for women) (11) and based on only one determination.

We also analyzed progression of ACR using traditional cutoff points for microalbuminuria (≥30 mg/g), and macroalbuminuria (≥300 mg/g). Progression of albuminuria was defined as a doubling of baseline ACR to at least 100 mg/g or worsening of ACR status on two or more visits (*i.e.*, progression from normal albuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria). We also analyzed progression including an additional category of low normal (<10 mg/g) and high normal (10–29.9 mg/g) albuminuria (12).

Statistical Analyses

Patients with baseline and at least two other annual measures of serum creatinine and ACR were included in the analysis. Baseline demographic and clinical data are presented for all 1799 participants, and data are presented by glycemic randomization (IS versus IP) in Table 1. Follow-up serum creatinine and ACR were considered to be at the same time point if they were within 3 months of each other. The measures closest to the patients' annual anniversary date were chosen and assessed for progression. Follow-up serum creatinine and eGFR were only measured in 2002 and 2003 for those participants taking metformin. Thereafter, they were measured yearly for all participants. Means and SDs are presented for continuous variables with normal distribution, medians and interquartile ranges (IQRs) are presented for continuous variables with non-normal distribution, and proportions are presented for categorical variables. Linear trends were tested using parametric and nonparametric methods. Likelihood based mixed models with a logit link and a random intercept were used to model renal progression during follow-up. The addition of a random slope to the logit models did not improve the models and was excluded.

Basic mixed models included time of measurement and baseline measures of eGFR and ACR along with the randomized treatment strategies. There were no significant interactions between the randomized glycemic and cardiac treatments in any of the models. Interactions between time of measurement and baseline eGFR or ACR were found not to be significant. Fully adjusted models included all elements of the basic models along with the *a priori* chosen variables of sex, race/ethnicity, diabetes duration, baseline body mass index, BP, insulin use, HDL and LDL cholesterol, triglycerides, smoking status, concurrent glycated hemoglobin, and angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) use to evaluate the independent effects of IS versus IP treatment on renal outcomes.

Missing values for baseline covariates in the fully adjusted models were replaced with the mean baseline values. All participants in this analysis had at least two follow-up visits; however, some had missing data. Pattern mixture model methods were used to assess the impact of missing data on the model estimate of interest (13). Patients were coded as completers, partial completers, or dropouts based on the completeness of their data. Completers had all expected data, partial completers had fewer measures than expected, and dropouts did not complete the study. The completeness indicators were added to the basic models, and interactions between the randomized treatment strategies and the indicators were assessed.

Nominal P values are reported. Because this report focuses on both ACR and eGFR, a Bonferoni correction of the P value (0.05/2=0.025) was used to determine statistical significance. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used for analyses.

Results

Of the entire study cohort of 2368 patients enrolled in BARI 2D, 1799 patients had baseline values and at least two additional yearly measurements of ACR and serum

Table 1. Baseline characteristics of patients randomized to insulin-sensitization therapy versus insulin-provision therapy

Characteristic	All Patients (*n*=1799)	IS (*n*=922)	IP (*n*=877)
Men, %	71.2	70.8	71.5
Age, yr (mean, SD)	62.0, 8.7	62.2, 8.9	61.9, 8.4
Race/ethnicity, %			
White non-Hispanic	66.7	66.5	66.9
Black non-Hispanic	15.5	15.0	16.0
Asian/other non-Hispanic	5.6	6.1	4.9
Hispanic	12.3	12.4	12.2
Duration of diabetes, yrs (median, IQR)	8.3, 3.6–15.0	8.0, 3.7–14.6	8.8, 3.5–15.5
Body mass index (mean, SD)	31.6, 5.8	31.6, 5.8	31.6, 5.8
Systolic BP mm Hg (mean, SD)	131.5, 20.4	131.3, 20.0	131.7, 20.8
Diastolic BP mm Hg (mean, SD)	74.8, 11.3	74.8, 11.4	74.7, 11.3
HbA1c, % (mean, SD)	7.7, 1.6	7.6, 1.6	7.7, 1.6
Urine albumin, mg/L (median, IQR)	12.0, 5.0–42.0	12.5, 5.0–42.0	12.0, 5.0–42.0
Urine creatinine, mg/dl (median, IQR)	99.0, 62.0–148.0	99.0, 62.0–147.0	99.0, 61.0–148.0
ACR, mg/g (median, IQR)	11.8, 5.1–43.6	11.5, 5.0–46.7	12.1, 5.3–41.3
Normal albuminuria, %	60.9	61.3	60.4
Microalbuminuria, %	30.1	29.9	30.3
Macroalbuminuria, %	9.0	8.8	9.2
Serum creatinine, mg/dl (median, IQR)	1.0, 0.9–1.2	1.0, 0.8–1.2	1.0, 0.9–1.2
eGFR, ml/min per 1.73 m^2 (mean, SD)	76.6, 20.1	77.0, 20.6	76.1, 19.5
eGFR<60, %	21.9	22.8	20.9
eGFR<60 and macroalbuminuria, %	3.8	4.3	3.3
Total cholesterol, mg/dl (mean, SD)	170.3, 41.1	168.9, 41.8	171.7, 40.4
HDL cholesterol, mg/dl (mean, SD)	38.2, 10.1	38.1, 9.9	38.4, 10.2
LDL cholesterol, mg/dl (median, IQR)	92.0, 74.0–116.0	91.0, 73.0–114.0	94.0, 75.0–118.0
Triglycerides, mg/dl (median, IQR)	148.0, 105.0–218.0	147.5, 101.0–216.0	149.5, 119.0–219.0
ACE/ARB use, %	77.2	76.7	77.7
TZD use, %	18.4	19.8	17.0
Metformin use, %	55.1	56.5	53.7
Insulin use, %	25.7	24.2	27.3
Sulfonylurea use, %	55.1	56.5	53.7

Insulin-sensitizing drugs included metformin, rosiglitazone, and pioglitazone. Insulin-providing drugs included insulin and sulfonylureas. IS, insulin sensitization; IP, insulin provision; IQR, interquartile range; HbA1c, hemoglobin A1c (glycated hemoglobin); ACR, albumin/creatinine ratio; eGFR, estimated GFR; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; TZD, thiazolidinedione.

creatinine. Baseline characteristics of 1799 patients are shown in Table 1. There were no significant differences in demographic, clinical, or laboratory values in those patients randomized to IS versus IP (Table 1). Comparison of baseline characteristics of 1799 study participants included in this analysis with 569 BARI 2D participants who were not included showed that those patients not included were slightly older, were more likely to use insulin, and had lower baseline eGFR compared with 1799 included participants. (Supplemental Material and Supplemental Table 1).

Diabetes Medications at Baseline and Follow-Up

Table 2 is a summary of diabetes medications at baseline and follow-up in patients randomized to the two different glycemic control strategies of IS and IP. The BARI 2D protocol was target-driven; to achieve a glycated hemoglobin level of <7%, investigators were permitted to add any clinically indicated drug if they failed to achieve the desired level after randomization to IS or IP. At 5 years, 82% of subjects randomized to IS were still on IS drugs; among these patients, one half were taking only IS drugs, and the remaining patients were taking a combination of IS and IP. A small number (14%) of those patients randomized to IS had completely crossed over and were taking only IP drugs. For subjects randomized to the IP strategy, at 5 years, 92.8% were still taking IP therapy, and among these patients, 77% were maintained on IP drugs only.

Eighteen percent of subjects randomized to IP were taking IS drugs at 5 years. By 6 months and thereafter, patients in the IS treatment arm compared with the IP treatment arm had significantly lower mean levels of glycated hemoglobin ($P<0.002$ for each time point; absolute difference=0.4%).

Changes in Albuminuria

Table 3 shows longitudinal median ACR and mean eGFR in the IS versus IP treatment groups at baseline and each year of follow-up. ACR increased from a median value of 11.5 (IQR=5.0–46.7) to 15.7 mg/g (IQR=6.2–55.4) at 5 years in the IS group (P value for trend<0.001) but remained stable in those patients treated with IP drugs: from 12.1 (IQR=5.3–41.3) to 12.4 mg/g (IQR=5.8–50.6).

Table 4 shows urine albumin and creatinine concentrations. Urine albumin concentration increased in both IS and IP groups, although the increase was greater in the IS group. Urine creatinine increased more in the IP group,

Table 2. Diabetes medication use at baseline and during follow-up

Glycemic Control Therapy	Randomized to IS (%)				Randomized to IP (%)			
	Baseline (*n*=922)	Year 1 (*n*=800)	Year 3 (*n*=813)	Year 5 (*n*=416)	Baseline (*n*=877)	Year 1 (*n*=569)	Year 3 (*n*=771)	Year 5 (*n*=417)
Neither IS nor IP	9.4	3.1	3.2	3.6	8.8	9.1	8.7	5.0
IS only	16.3	63.5	54.2	43.5	15.8	0.7	1.2	2.2
IP only	26.7	2.8	7.4	14.4	30.7	80.7	80.9	77.0
Both IS and IP	47.4	30.6	35.2	38.5	44.7	9.5	9.2	15.8
IS drug class								
No TZD or metformin	36.3	6.4	9.1	16.8	39.6	90.3	90.5	87.9
TZD but no metformin	7.4	6.9	12.2	10.7	5.6	0.5	0.9	1.0
Metformin but no TZD	44.0	23.5	26.5	30.0	43.4	7.4	6.8	9.2
Both TZD and metformin	12.4	63.3	52.2	42.4	11.4	1.8	1.8	1.9
IP drug class								
No insulin or sulfonylurea	26.2	67.0	59.3	51.7	25.6	12.1	11.3	8.5
Sulfonylurea but no insulin	49.7	11.8	13.7	14.4	47.1	37.4	29.0	23.0
Insulin but no sulfonylurea	17.2	19.0	23.3	29.0	20.7	32.7	35.4	43.3
Both insulin and sulfonylurea	6.9	2.3	3.7	4.9	6.6	17.8	24.3	25.2
ACE-I or ARB	76.7	90.0	91.6	89.3	77.6	91.2	92.7	92.3

IS, insulin-sensitizing drugs; IP, insulin-providing drugs; TZD, thiazolidinedione; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3. Median values of albumin/creatinine ratio and estimated GFR at each year of follow-up in patients randomized to insulin-sensitizing drugs versus insulin-providing drugs

Time of Follow-Up	Albumin/creatinine ratio (mg/g)				Estimated GFR (ml/min per 1.73 m^2)			
	IS		IP		IS		IP	
	N	Median (IQR)	*N*	Median (IQR)	*N*	Mean (SD)	*N*	Mean (SD)
Baseline	922	11.5 (5.0–46.7)	877	12.1 (5.3–41.3)	922	75.0 (20.6)	877	76.1 (19.5)
Year 1	800	13.2 (6.1–45.5)	569	11.6 (5.4–40.5)	800	70.6 (20.6)	569	74.4 (20.2)
Year 2	820	14.7 (6.2–59.4)	733	12.2 (5.2–46.0)	820	70.8 (21.5)	733	70.2 (21.6)
Year 3	813	14.8 (6.2–52.9)	771	12.9 (5.5–46.3)	813	68.3 (21.9)	771	67.7 (20.9)
Year 4	687	16.4 (6.0–63.5)	672	11.6 (5.3–50.3)	687	66.9 (21.6)	672	66.8 (21.4)
Year 5	416	15.7 (6.2–55.4)	417	12.4 (5.8–50.6)	416	66.3 (22.6)	417	66.8 (21.1)
P value for trend		<0.001		0.21		<0.001		<0.001

IS, insulin-sensitizing drugs; IP, insulin-providing drugs; IQR, interquartile range.

particularly in the early years of the study. Thus, some of the stability of ACR in the IP group may have been caused by an increased urine creatinine concentration. The proportions of patients with macroalbuminuria were similar in the IS versus IP group at each follow-up year (Table 5).

Randomization to IS compared with IP was associated with increased risk for progression of ACR, regardless of whether traditional cutoff points or sex-specific cutoff points for albuminuria were used (odds ratio [OR], 1.59; 95% confidence interval [95% CI], 1.25 to 2.02; $P<0.001$ for sex-specific cutoff points) (Table 6). After adding the category of high normal albuminuria (10–29.9 mg/g) to the analysis, ACR progression was still greater in IS versus IP (Table 6 and Supplemental Table 2). After adjustment for systolic and diastolic BP, body mass index, level of glycated hemoglobin, smoking status, lipids, and ACE-I or ARB use, the effect of IS compared with IP on albuminuria progression did not change (OR, 1.76; 95% CI, 1.37 to

Table 4. Median yearly urine albumin concentration and urine creatinine concentration in patients randomized to insulin-sensitizing drugs versus insulin-providing drugs

Time of Follow-Up	Urine Albumin (mg/L)				Urine Creatinine (mg/dl)			
	IS		IP		IS		IP	
	N	Median (IQR)	*N*	Median (IQR)	*N*	Median (IQR)	*N*	Median (IQR)
Baseline	922	12.5 (5.0–42.0)	877	12.0 (5.0–42.0)	922	99.0 (62.0–147.0)	877	99.0 (61.0–148.0)
Year 1	800	15.0 (5.0–49.0)	569	13.0 (5.0–43.0)	800	104.5 (69.0–148.0)	569	107 (64.0–154.0)
Year 2	820	15.5 (6.0–55.0)	733	15.0 (5.0–52.0)	820	100.1 (64.0–146.5)	733	111.0 (74.0–161.0)
Year 3	813	15.0 (6.0–54.0)	771	15.0 (6.0–52.0)	813	102.0 (64.0–148.3)	771	110.0 (73.0–155.5)
Year 4	687	17.0 (6.0–65.0)	672	14.0 (5.0–56.5)	687	103.3 (64.0–153.0)	672	104.2 (65.5–156.5)
Year 5	416	17.0 (6.0–59.0)	417	15.0 (6.0–60.0)	416	104.7 (66.0–154.5)	417	111.5 (72.7–161.6)
P value for trend		<0.001		0.03		0.35		0.007

IS, insulin-sensitizing drugs; IP, insulin-providing drugs; IQR, interquartile range.

Table 5. Proportion in each randomized treatment group with macroalbuminuria and reduced estimated GFR at each year of follow-up

Time of Follow-Up	Macroalbuminuria				Reduced eGFR (eGFR<60 ml/min per 1.73 m^2)			
	IS		IP		IS		IP	
	N	Percent	*N*	Percent	*N*	Percent	*N*	Percent
Baseline	922	8.8	877	9.2	922	22.8	877	20.9
Year 1	800	8.3	569	9.3	800	26.3	569	25.5
Year 2	820	10.4	733	10.4	820	33.4	733	32.9
Year 3	813	10.8	771	9.7	813	35.3	771	37.0
Year 4	687	10.3	672	9.7	687	39.0	672	38.2
Year 5	416	9.6	417	10.6	416	38.7	417	40.8

Sex-specific cutoff points for macroalbuminuria were used: ≥250 mg/g for men and ≥355 mg/g for women. eGFR, estimated GFR; IS, insulin-sensitizing drugs; IP, insulin-providing drugs.

Table 6. Odds ratios for progression of albuminuria in patients treated with insulin-sensitizing drugs compared with insulin-providing drugs in unadjusted and adjusted models

Albuminuria Category Definition	IS Versus IP OR	95% CI	*P* Value	IS Versus IP Adjusted OR	95% CI	*P* Value
Standard cutoff points	1.32	1.02 to 1.70	0.03	1.47	1.13 to 1.92	0.004
Four-category model	1.48	1.19 to 1.85	<0.001	1.63	1.29 to 2.04	<0.001
Sex-specific cutoff points	1.59	1.25 to 2.02	<0.001	1.76	1.37 to 2.25	<0.001

ORs for progression of albuminuria using different cutoff points for micro- and macroalbuminuria are shown. The standard cutoff point shows the OR for albumin/creatinine ratio progression in IP- versus IS-treated patients when albumin/creatinine ratio progression is defined as a doubling of the albumin/creatinine ratio to at least 100 mg/g or a change in category (from normal to microalbuminuria [≥30 mg/g] or from micro- to macroalbuminuria [≥300 mg/g]). The four-category model includes the additional categories of low normal (<10 mg/g) and high normal (10–29.9 mg/g) albuminuria as well as micro- and macroalbuminuria. The sex-specific cutoff points show the OR for albumin/creatinine ratio progression using sex-specific cutoff points for albuminuria (microalbuminuria=17–250 mg/g for men and 25–355 mg/g for women). Each model also includes year of follow-up, baseline estimated GFR, and baseline albumin/creatinine ratio. Each adjusted model also includes year of follow-up, baseline estimated GFR, baseline albumin/creatinine ratio, sex, race/ethnicity, diabetes duration, baseline body mass index, baseline BP, baseline insulin use, HDL and LDL cholesterol, triglycerides, smoking status, and concurrent hemoglobin A1c (glycated hemoglobin) and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use. IS, insulin-sensitizing drugs; IP, insulin-providing drugs; OR, odds ratio; 95% CI, 95% confidence interval.

2.25; $P<0.001$) (Table 6). There were no differences in ACR progression in patients taking only thiazolidinedione (TZD) compared with patients taking only metformin; however, the number of subjects on monotherapy was small.

Over one half of patients had normal albuminuria at baseline (60.8%); of these patients, 39.5% progressed to microalbuminuria at any time (43.2% in the IS group and 35.7% in the IP group; $P=0.01$), and 2.7% progressed to macroalbuminuria at any time (4.1% in the IS group and 1.3% in the IP group; $P=0.005$). In patients with baseline microalbuminuria, 25% progressed to macroalbuminuria (27% in the IS group and 23% in the IP group; $P=0.26$). In those patients with baseline microalbuminuria (36%), 29.5% regressed to normal albuminuria (27.2% in the IS group and 32.0% in the IP group; $P=0.22$); among those patients who entered with macroalbuminuria (9%), 36% regressed in the IS group, and 35% regressed in the IP group ($P=0.87$).

Changes in eGFR

eGFR declined similarly in patients treated with either IS or IP: from 75.0±20.6 to 66.3±22.6 ml/min per 1.73 m^2 (P value for trend<0.001) in the IS group and from 76.1±29.5 to 66.8±22.1 ml/min per 1.73 m^2 (P value for trend<0.001) in the IP group. At the end of 5 years, the proportion of individuals with eGFR<60 ml/min per 1.73 m^2 almost doubled in both the IS and IP groups (Table 5). Only 1.8% ($n=35$) of the study cohort developed ESRD (need for renal replacement therapy or eGFR≤15 ml/min per 1.73 m^2), with equal numbers in the IP ($n=18$) and IS ($n=17$) groups. The OR for worsening eGFR was 1.13 (95% CI, 0.92 to 1.38; $P=0.23$) for patients randomized to IS compared with IP.

Meaningful comparisons of worsening of eGFR could not be made between patients treated with TZD alone compared with metformin alone because of the small numbers of patients on monotherapy. Only 82 subjects (9.8%) were on TZD alone at least 50% of the time, whereas 228 subjects (27%) were on metformin alone.

Sensitivity Analyses

We performed additional analyses of ACR and progression of worsening of eGFR and incorporated indicators for completeness of data (Supplemental Material and Supplemental Table 3). The ORs for ACR progression in the IS group versus the IP group were 1.37 (95% CI, 1.00 to 1.88) for patients with complete data, 1.94 (95% CI, 1.31 to 2.88) for patients who completed the study but did not have all required data, and 0.79 (95% CI, 0.18 to 3.43) for patients who did not complete the study but had at least two follow-up visits (Supplemental Material and Supplemental Table 3). These ORs are not significantly different ($P=0.27$).

ACR progression was analyzed separately in participants randomized after January 1, 2003, after which time all subjects had serum creatinine measured yearly. The OR for ACR progression for IS versus IP was 1.44 (95% CI, 1.07 to 1.93; $P=0.02$), similar to the analysis that included participants randomized before and after 2003 and results using all urine specimens collected, including those results randomized between 2001 and 2003 (even if serum creatinine was not available) (Supplemental Material and Supplemental Table 4).

The ORs for worsening eGFR in the IS group versus the IP group were 1.08 (95% CI, 0.80–1.43) for completers, 1.27 (95% CI, 0.91–1.77) for partial completers, and 0.93 (95% CI, 0.29–3.00) for patients who did not complete the study ($P=0.72$ for differences among three ORs).

Discussion

Given the enormity of the public health problem of kidney disease in patients with T2DM, renal protection attributable to a particular glycemic control strategy would significantly impact practice. The BARI 2D trial, a comparison of IS therapy with IP therapy in patients with T2DM, CAD, and baseline serum creatinine<2 mg/dl, offered a unique opportunity to examine the impact of almost universally used therapies on important renal outcomes. We found that eGFR declined steadily and similarly over time in both treatment groups. Despite slightly better glycemic control in patients randomized to IS, there was a small but statistically significant increase in median ACR over time and a significantly higher risk of progression of ACR compared with patients treated with primarily IP therapy, in whom albuminuria remained stable. A significantly greater proportion of those patients with normal albuminuria at baseline progressed to either microalbuminuria or macroalbuminuria in the IS group compared with the IP group. Because the primary outcomes of BARI 2D (death and cardiovascular disease) were not significantly different in patients treated with IS versus IP (6), the impact of glycemic control treatment on renal outcomes was not confounded by differential effects on patient survival.

Although patients with a serum creatinine≥2 mg/dl were excluded from the BARI 2D trial, 43% of the cohort had evidence of kidney dysfunction at baseline (7). The rate of progression of ACR and worsening eGFR was relatively low but similar to the rates in other clinical trials of patients with T2DM, in whom glycemia, BP, and lipids were aggressively managed. The mean decrease in eGFR over 5 years in the BARI 2D trial was approximately 10 ml/min per 1.73 m^2, and very few patients developed ESRD; 90% of patients were treated with either ACE-Is or ARBs, which may explain the smaller than expected increases in albuminuria. Albuminuria improved in a subset of patients, but there were no differences in the rates of regression between IS- and IP-treated patients.

Our finding that albuminuria was more likely to increase in patients treated with IS versus IP was somewhat surprising given the strong experimental evidence from both preclinical models and clinical studies suggesting that insulin-sensitizing drugs, such as metformin and TZDs, would provide additional benefits because of anti-inflammatory and antithrombotic effects (14). Sobel *et al.* (15) reported that, in BARI 2D subjects, IS as opposed to IP treatment led to changes in biomarker profiles that were indicative of a profibrinolytic, antithrombotic, and anti-inflammatory state. Peroxisome proliferator-activated receptors are widely expressed in the kidney, and peroxisome proliferator-activated receptor gamma agonists have renoprotective effects in experimental models of diabetic kidney

disease (16,17). Administration of TZDs to insulin-deficient and -resistant diabetic rats ameliorated albuminuria and histologic hallmarks of diabetic nephropathy (18,19). Despite the robustness of preclinical data, the results in humans have been less encouraging (4). Insulin resistance is an independent predictor of worsening renal function (20); however, evidence that treatment of metabolic syndrome with insulin-sensitizing drugs is renoprotective is limited (21). Short-term clinical trials and a meta-analysis reported a reduction in albuminuria and BP with TZDs (22,23). In the Diabetes Outcome Progression Trial (ADOPT) study, there was a significantly smaller rate of rise in ACR and a greater rise in eGFR in those patients treated initially with rosiglitazone compared with metformin or glyburide, but there was no significant change in development of new onset of microalbuminuria or reduced eGFR after 5 years (24). In the BARI 2D trial, we did not find a clear benefit of one glycemic control strategy over another strategy, and although the differences were small, participants randomized to drugs that improve insulin resistance had a significantly greater risk of worsening albuminuria compared with those participants treated primarily with insulin or sulfonylureas. Although the clinical significance of worsening albuminuria in IS compared with IP remains unknown, our findings have implications for clinical practice and future studies of treatment of T2DM.

The strength of the BARI 2D study is the large, aggressively treated, well described population of patients with T2DM and CAD followed for up to 5 years. A limitation was the difficulty maintaining participants on either IS or IP alone without the addition of drugs from the other strategy. Few subjects were on monotherapy; thus, comparisons of renal outcomes attributable to individual drugs were not possible. However, we emphasize that the study design was a comparison of glycemic control strategies, reflecting what is often necessary in clinical practice. The goal was to achieve a target glycated hemoglobin of 7% within the IS or IP strategy, and although most patients remained on their randomized treatment assignment (82% in the IS group and 92.8% in the IP group), inevitably, there was less than complete differentiation of treatment regimens. In patients randomized to IS, 38% required the addition of IP drugs, and in those patients randomized to IP, 16% had IS drugs added. Although the use of combination regimens may have undermined the full appreciation of differences related to IS versus IP regimens, our study has the distinct advantage of being generalizable to diabetic patients at large, most of whom are managed with combination therapy.

We acknowledge additional limitations. The BARI 2D study was powered to detect differences in cardiovascular outcomes rather than renal outcomes. Although we observed a small but significant increase in ACR progression in participants randomized to IS, the study may have been underpowered to detect small differences in worsening of eGFR that may have been caused by IS or IP. Also, by the end of 5 years, almost one half of the patients in both groups were not available for follow-up because of death (12%) or unavailability of 5-year follow-up data caused by later enrollment. Other limitations were the use of a single annual (*i.e.*, no rapid confirmation) urine specimen for determination of albuminuria status and the required presence of significant CAD, thereby limiting the application of these results to more general populations of patients with T2DM. This study was performed before wide adaptation of the isotope dilution mass-spectrometry traceable creatinine assay; thus, variability of the serum creatinine levels at local laboratories is another limitation. These limitations notwithstanding, the BARI 2D study remains the largest study to date evaluating the impact of IS versus IP regimens on two important renal outcomes (albumin excretion and eGFR) in a large population of T2DM patients managed uniformly in the context of a randomized trial.

In summary, in the BARI 2D trial, despite slightly lower glycated hemoglobin levels over 5 years in patients randomized to the IS group, there was evidence for a greater increase in albuminuria associated with IS compared with IP and a similar degree of worsening eGFR in both treatment arms.

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A complete list of the BARI 2D Study Group can be found in the Supplemental Appendix at NEJM.org (*N Engl J Med* 360: 2503–2515, 2009).

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